Receptor theory

- **Main points:**
  1) Concept of receptors
  2) Classification of receptors
  3) Transducer mechanism
  4) Receptor target site- response
  5) Types of antagonism
  6) Main definition of pharmacodynaic aspects

Pharmacokeinetic means absorption, distribution, metabolism and excretion.
Pharmacodynaic is the mechanism of action of the drugs, It has two parts:-

1) qualitative part: drug action.
2) quantitative part: drug dose response.

- **QUALITATIVE:**

- how can the drug be introduced to the body and give its respose.
- Suppose you have an oral drug, it is absorbed and distributed and it reaches it site of action.
- Liver infection pt. took a drug it will be distributed through the whole body, brain, kidney, but the problem is in the liver so the site of action is the liver.
- 2nd pt. with kidney disease, maybe retension of Na and water then he has oedema, when he takes the drug, it will reach all the sites and also the kidney and this will be its site of action of the drug.
- 3rd pt. problem is in nervous system, he has hypertention due to incease nor adrenaline seretion from neurons so the site of action of the drug is the neurons.

In the site of action, the drug also reaches cellular site of action, the functional unit of the organ. If pt. has bacteria in liver, cellular site of action is bacteria in hepatocytes.

- Cellular site of action is either on cell membrane, within cells or outside cells

When the drug acts on cell membrane, it has receptors (lock and key), may be ion channels, Ca, Na and so on, or act on enzymes.

- In cells, drug acts on DNA, may destroy DNA like anticancer drugs, interact in the nucleus of the cell, or protein carrier (protein transport drug from inside to outside the cell) e.g. renal tubular cells.
- OCT(organic cation transporter): for basic drugs, OAT(organic anion transporter): for acidic drugs(These two system found in tubular cell in kidney).

- (Probenecid Pb and penicillin Pn drug interaction) Both are acids transported with OAT, probenecid has high affinity more than penicillin for the carrier, Probenecid will be secreted and penicillin will be moved back into blood, so concentration of penicillin will increase maybe increasing its effect or toxicity depending on the dose.
- The basic for all drugs that are displaced or interfere with carrier for transport in kidney, GIT, LIVER… Depend on which has more affinity to transporter.
- Outside cells, chemical or physical reactions Chemical, e.g. antacid: aluminum hydroxide Al(OH)3. If pt. has dyspepsia, HCl increases in stomach, drink milk of magnesia contains Al(OH)3 and Mg(OH)2 to neutralize, and relief the pt.
$Al(OH)3 + HCl \rightarrow Al(Cl)3 + H2O$ salt and water neutralization.
- This to treat dyspepsia or heartburn it consumes all Cl. Al(OH)3 decreases the activity of HCl acts as antagonist. So one type of antagonism is chemical reaction.
- e.g. overdose of heparin, for clot to increase bleeding, so we give drug to decrease its side effect, Protamine, Heparin is negative and protamine is positive so they will interact form a complex and decrease heparin overdose toxicity.
- Chemical reaction can be used Not only to treat but also for poisoning and overdose.
- Other e.g. iron overdose dysferoxamine antidote, it is antagonist, drug that will decrease the toxicity of poison or drug overdose.
- Basic drug, Morphine excreted by OCT transporter. If large amount of morphine is present in the urine, so we decrease toxicity by making the urine acid and the base will be ionized, attracts the proton that present in the medium, so become ionized and the ionized drug cannot pass through the membrane, Why? Because it binds will negative proteins on cell membrane and doesn't enter the cell. So if we want to use an ionized drug as a treatment we give it parenterally to give their activity through the blood .
- Unwanted effect, milk and tetracycline, decrease the effect of tetracycline by binding to the calcium bivalent each will bind with different tetracycline forming complex that cannot pass through the cell membrane, therefor the complex formation by milk and tetracycline leads to decrease absorption of tetracycline.
- In summary, the outside of the cell can be chemical reaction like antacid … for treatment of disease, disorders, poisoning, or undesired effect.

Physical.

- e.g. charcoal is powder from coal used for the treatment of poisoning, by only physical reaction. It is powder and on its surface there is pores, like a sponge when passed on water there will be adsorption not absorption, this means that charcoal composes of pores that bind the poison, morphine unabsorbed in the GIT.

- If we said charcoal decreases the poisoning of absorbed morphine, this is false. Because charcoal only works in GI lumen to bind or adsorb morphine, unabsorbed morphine leads to decrease morphine and then it is excreted by feces to outside the body.
- Magnesium sulfate, mannitol, read about it in your book. Diuretics to increase the discharge of urine.
- The cells can be of our body, or virus or bacteria, Coming back to our 3 pt.
    1) liver disease, viral infection, used a drug, kill the viral infection. The action of drug is cytotoxic action because it killed the bacterial and viral invaders.
    2) Edema because of the kidneys, used diuretic e.g. furasamide, leads to decrease in edema. So the action of drug is change. Normal urine, anuria oliguria, high urine, normal urine. So it only caused change,
    3) Sympathetic nervous system release noradrenaline that works on the vessels causing vasoconstriction, increasing blood pressure this leads to hypertension. To treat tis pt. we give him a drug that acts on vasculature leads to block these contractions so decrease blood pressure. So the action here is change
    4) Pt. with type 1 diabetes, no insulin, treat with insulin. The action here is replacement.
- So main principle of the drugs is:
    1- Modification.
    2- Replacement. Hypothyroidism, give thyroid
    3- Cytotoxic action. Cancer, give anticancer.
- What is receptor; receptors are macromolecular that bind ligand and translate this binding into pharmacological or biological response. Two functions:
    1- binding to the ligand, it should be from the same size and same length.
    2- And translate this binding into biological or pharmacological or biological effect.
- They are located in the cell, on the cell membrane or outside the cell. There are a lot of receptors, e.g. albumin, some drugs have the affinity to bind to albumin, so albumin is silent receptor because its binding with the drug doesn't produce function of drug. When the drug concentration decreases the albumin release the drug to balance its concentration.
- Ligand can be endogenous, like epinephrine, norepinephrine, histamine, acetyl choline, hormones, all that are working in our body as transmitters or mediators are endogenous ligand for the receptors.
- Exogenous, drug, poison anything from air, allergens.
- Transducer mechanism, between the binding side and the biological response.
- And it is what differentiate the function of one receptor from the other, maybe two receptors have the same binding site they have different transducer mechanisms this leads to difference in the response.

***- classification of the receptors*:-**

1)Selective drugs : only bind to specific receptor in specific cell to produce specific effect.

2)Non-selective drugs: bind to many receptors on different cells(cells of kidney,GIT,eye)and produce different effects.

-Note: the selective drug has less toxicity and less undesired effects ,but the non-selective drug has more toxicity and more undesired effects.

-Ex:-

1- promethazine (phenergan)which is used for nausea and vomiting ,the desired effect is to block dopamine receptor (antivomiting),and the other effects are to block histamine effect receptor (antiallergic), block muscarinic receptor, promethazine is classified as antihistaminic drug.

2- Diphenhydramine: act on muscarinic receptors, sedation (antihistaminic action).

- So the 2drugs are non-selective.
- Now we have the A.N.S which is divided to S.N.S. and P.N.S.
- Adrenergic receptors = sympathetic system has transmitters(noradrenaline, adrenaline, dopamine)which act on α1, α2, β1, β2, β3 receptors to produce the response such as increase heart rate, bronchodilation and used also in fight and flight.
- Cholinergic system =parasympathetic system has only one transmitter(acetylcholine)which act on M(muscarinic) andN(nicotinic)receptors and give the response.

- ***Classification of receptors according to the location :-***

1) Receptors are located at the SNS,so the receptors called adrenergic receptors(α1,α2,β1,β2,β3).

2) Cholinergic receptors which are muscarinic and nicotinic receptors.

3) Dopamine receptors are sympathetic receptors and also has specific neurons in CNS andPNS(D1, D2), so dopamine has 4receptors (D1, D2, α1, β).

4) Histamine receptors:-

a) H1(located in CNS & PNS) in CNS lead to increase wakefulness, regulate appetite and in cognition(memory)and in PNS lead to bronchoconstriction, vasodilation and in sensory nerve increase pain and itching.

b) H2 (only act on parietal cells in stomach that stimulate acid secretion which may lead to gastritis), so H2 blockers are used in treatment of gastric and peptic ulcers.Also lead to vasodilation that help in anaphylactic shock and itching.

- All these responses lead to inflammation, because inflammation (increase or decrease histamine), so when histamine release act central to cause nervousness and peripheral cause vasodilation that lead to edema then heating and other signs of inflammation.

- The patient who has done allergic or anaphylactic reaction can be treated with drug stop the histamine(antihistaminic anti H1drug), but in anaphylaxis is very serious which may lead sometimes to hypotention and here we give adrenaline.
5) 5-hydroxytryptamine receptors (serotonine) that has a lot of receptors (1,2,3,4) and each receptor has subtypes and also each subtype has specific function (that is difficult to read it) So nausea and vomiting result from dopamine receptors, 5-HT (serotonin) receptors. Here we have one example ondansetrone that block 5-HT3 to decrease nausea and vomiting which given by anticancer drug or by any other illness.
- Most of receptors ate peripheral receptors 90% and 10% of them are central receptors.
- we can find transmitters which called mediators that work between the neurons in CNS.

- Central receptors mainly are:

1) **Amino acid receptors**:
   - GABA, glycine (inhibitory receptors).
   - Aspartate, glutamate (excitatory receptors).
2) **Peptide receptors**:
   enkephalins endorphins (endogenous morphine)is peptide act like morphine that modulate pain perception, motor behavior and enemies, produce sedation and addiction.

- These peptides are released when there is stress such as car accident or someone has fraction, so when lesion of this car accident or the fraction is threaded , the patient won't feel the pain because the body secrets these endogenous morphine which act on receptors of morphine.

- Structural classification of receptors (according to A.A.) :-

- these receptors are four families:
  1) Ligand gated ion channels such as nicotinic receptors, GABA, and so on.
  2) G- protein coupled receptors (guanine binding) such as muscarinic receptors and others.
  3) Ligand regulated enzyme (having enzyme property)like peptide hormone.
  4) Protein synthesis regulating receptors like steroid hormones.
- Peptide hormones are insulin, growth hormone
- Steroid hormones are glucocorticoids, androgen, estrogen, thyroxine, vitamin D, vitamin A.
- **Transducer mechanisms**:-

From conformational changes to products formation.
G-protein coupled receptor: 5 steps:

1) G-protein bind with the ligand to form complex.
2) Formation of conformational changes and activation of G- protein action.
   -There are two types of G-proteins: Gi (inhibitor), Gs (stimulator).
3) Activation of effector system (usually enzyme, e.g. adenylcyclase), this step happens if the G2 was activated in step 2.

4) Production of the second messenger (cAMP).
5) Activation of protein kinase, produce biological responses.

Example of transducer mechanism, Adrenaline acts on cardiac myocytes:

1) Binds to β1 receptors on heart (formation of complex).
2) Conformational changes and Gs protein activation.
3) Activation of effector system (adenylcyclase).
4) Production of second messenger (cAMP).
5) Activation of protein kinase.

- Biological effect: activation of troponin protein, that couple the actine and myocine, increase contractility of the heart.
- Acetyl choline:
  1) Ach bind to muscarinic receptor (M2).
  2) Conformational changes .
  3) Activation of G inhibitor.
  4) Biological effect: relaxation of cardiac muscle.
- So adrenaline and acetylcholine (2endogenous agonists) inside the body bind to different receptors on the same cells(same cardiac muscle) or same biological system and produce opposite action,this is called **physiological antagonism or functional antagonism**.
- So**, Physiological antagonism:-**

  Two drugs act on different receptors by different mechanisms, but have opposite effects on the same physiological system.

- Examples:

1- Histamine and adrenaline on bronchial muscles and blood pressure
2- Glucagon and insulin on blood sugar system
3- Adrenaline and acetyl choline: two endogenous agonists bind the same cells, same biological system but produce different effects

- Important definitions:

- Affinity: ability of the ligand(endogenous or exogenous) to bind to the receptor and form a complex.
- Intrinsic efficacy: ability of ligand to produce complete conformation change (no relation to dose.)
- example:-Adrenaline bind to receptor and produce 100% efficacy.
- If there is affinity + 100% efficacy = agonist drug.
- If there is affinity + less than 100% = partial agonist drug.
- If there is affinity + 0% efficacy = antagonist drug.
- Antagonists just bind and block the receptor, no action.
- E.g. antihypertensive drugs, block the receptor, prevent the continuous muscle contraction of blood vessels with time, gradually leads to decrease in blood pressure , because if the action occur, the muscle won't work after a period of time and become fattish.

- Receptor- Site-Response.(from the lecture of receptor theory):-

- note:- the drugs mostly block the prominent receptors on cells on the organ such asα1 Is more prominent in vascular smooth muscle than α2, so the drug will act mostly on α1.
- Hypertensive patient will treated with:-

1) antagonist α1Which decrease the vasoconstriction that lead to decrease blood pressure(α1 Blocker).

2) antagonist β1Which in turn act on:-

a) heart by decrease cardiac output that lead to decrease blood pressure.

b) kidney by decrease renin release which decrease angiotensin 2 secretion that lead to decrease blood pressure.